

ORIGINAL ARTICLE

Long-Term Results of Carotid Stenting versus Endarterectomy in High-Risk Patients

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ABSTRACT

BACKGROUND

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*The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPHIRE) investigators are listed in the Appendix.

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We previously reported that, in a randomized trial, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy for the treatment of carotid artery disease at 30 days and at 1 year. We now report the 3-year results.

METHODS

The trial evaluated carotid artery stenting with the use of an emboli-protection device as compared with endarterectomy in 334 patients at increased risk for complications from endarterectomy who had either a symptomatic carotid artery stenosis of at least 50% of the luminal diameter or an asymptomatic stenosis of at least 80%. The prespecified major secondary end point at 3 years was a composite of death, stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1080 days (3 years).

RESULTS

At 3 years, data were available for 260 patients (77.8%), including 85.6% of patients in the stenting group and 70.1% of those in the endarterectomy group. The prespecified major secondary end point occurred in 41 patients in the stenting group (cumulative incidence, 24.6%; Kaplan–Meier estimate, 26.2%) and 45 patients in the endarterectomy group (cumulative incidence, 26.9%; Kaplan–Meier estimate, 30.3%) (absolute difference in cumulative incidence for the stenting group, –2.3%; 95% confidence interval, –11.8 to 7.0). There were 15 strokes in each of the two groups, of which 11 in the stenting group and 9 in the endarterectomy group were ipsilateral.

CONCLUSIONS

In our trial of patients with severe carotid artery stenosis and increased surgical risk, no significant difference could be shown in long-term outcomes between patients who underwent carotid artery stenting with an emboli-protection device and those who underwent endarterectomy. (ClinicalTrials.gov number, NCT00231270.)

THERE IS A DIRECT RELATIONSHIP BETWEEN the degree of carotid artery stenosis and the risk of ipsilateral stroke.^{1,2} Carotid revascularization by means of carotid endarterectomy has proved highly successful in reducing the incidence of stroke among patients with moderate-to-severe symptomatic carotid stenosis¹ as well as among those with severe asymptomatic carotid stenosis.³ Although carotid endarterectomy has been considered the gold standard for the treatment of carotid stenosis for decades, carotid artery stenting has emerged as an alternative type of treatment for this common disorder.^{4,5} The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study⁶ involved the random assignment of patients at high surgical risk, owing to anatomical characteristics or co-existing conditions, to undergo either protected carotid artery stenting or carotid endarterectomy. The trial showed that carotid artery stenting was not inferior to carotid endarterectomy in this population at 1 year. Subsequently, reports of several nonrandomized studies evaluating the short-term safety of protected carotid artery stenting have been published.^{7,8}

It remains unclear whether carotid stenting provides the same degree of protection against stroke as does carotid endarterectomy over the long term. Since the main clinical benefit of carotid revascularization is protection against future stroke, it is important to compare long-term outcomes between the two types of surgery. To assess the relative durability of the two strategies with respect to ischemic events and the need for revascularization, we report the prespecified secondary end point of safety and efficacy outcomes at 3 years (1080 days) in the randomized cohort from the SAPPHIRE trial.

METHODS

The methods, design, and 1-year outcomes of the SAPPHIRE trial have been reported previously.⁶ This prospective, randomized, multicenter trial was conducted in compliance with the provisions of the Declaration of Helsinki, was performed under an investigational-device exemption granted by the Food and Drug Administration, and was approved by the institutional review boards of all participating institutions.

The study was funded by Cordis, the study sponsor. The sponsor had advisory input into the study design and had representation on the execu-

tive committee. Monitoring at the clinical sites was provided by an independent monitoring group, under the supervision of the sponsor. The data were held at the Harvard Clinical Research Institute; the investigators had full access to the data for analysis and reporting. The authors conducted the analyses, made the decision to publish the results, and wrote the manuscript. The executive committee and authors vouch for the veracity and completeness of the data. The sponsor reviewed the manuscript and had an opportunity for comment.

TRIAL DESIGN

The trial was conducted at 29 centers; enrolled patients were at least 18 years of age, had been referred for treatment of a carotid artery stenosis, and were deemed to be at high surgical risk for complications from carotid endarterectomy. All patients provided written informed consent. Inclusion criteria were the presence of one or more criteria for high surgical risk and a stenosis of more than 50% of the luminal diameter in patients with symptoms or a stenosis of more than 80% in those without symptoms. The criteria for high surgical risk were clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal-nerve palsy, recurrent stenosis after carotid endarterectomy, previous radical neck surgery or radiation therapy to the neck, and an age of more than 80 years.

All patients received aspirin and were given a therapeutic dose of heparin during the procedure. Carotid endarterectomy was performed according to the surgeon's preferred technique. Patients in the stenting group received clopidogrel before the procedure and for 2 to 4 weeks thereafter. Stenting was performed with the use of a self-expanding, nitinol stent (Smart or Precise, Cordis) and an emboli-protection device (Angioguard or Angioguard XP Embolic Capture Guidewire, Cordis). Clinical follow-up, including a full neurologic examination by an independent neurologist, was required within 24 hours after the procedure and daily until discharge, as well as at 30 days, 6 months, 1 year, and annually thereafter for a total of 3 years.

END POINTS

The trial had a noninferiority design and a primary end point of the cumulative incidence of death,

stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. Yearly follow-up through 3 years was prespecified, but the statistical comparison for noninferiority at later intervals was not specified. The prespecified major secondary end point considered in this report includes the primary-end-point events plus death or ipsilateral stroke between 1 and 3 years. For the purpose of statistical analysis, 1 year was defined as 360 days, 2 years as 720 days, and 3 years as 1080 days.

Death was defined as death from any cause. It was further categorized as death from cardiac causes, from neurologic causes, or from other causes. Stroke was defined as any focal nonconvulsive neurologic deficit in a vascular territory that persisted for more than 24 hours. Strokes were classified as major or minor on the basis of the National Institutes of Health Stroke Scale, the Barthel index of functional levels in activities of daily living, and the Rankin scale of functional disability. Myocardial infarctions were classified as Q-wave (new pathologic Q waves in two or more contiguous electrocardiographic leads) or non-Q-wave (elevation of the creatine kinase level to more than twice the upper limit of the normal range, with a positive MB fraction). Target-vessel revascularization was defined as repeat percutaneous or surgical treatment of the carotid artery performed for either ischemic neurologic symptoms and a stenosis of at least 50% of the luminal diameter or a stenosis of at least 80% but not neurologic symptoms. The severity of stenosis was determined angiographically according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.⁹

STATISTICAL ANALYSIS

Data were submitted to the data coordinating center (Harvard Clinical Research Institute, Harvard Medical School, Boston), where the analyses were performed. The effectiveness analysis and safety evaluation were performed with the use of data for the intention-to-treat population. Categorical data were compared between the two treatment groups by means of Fisher's exact test. The 95% confidence intervals for the absolute difference in percentages between the endarterectomy group and the stenting group were estimated with the use of the normal approximation to the binomial distribution. The analysis at 3 years involved the comparison of the cumulative incidences of the pre-

specified major secondary end point between the two groups for all patients who underwent randomization. The interaction of clinical center and treatment assignment was estimated in order to confirm that the results could be pooled among the enrollment sites ($P=0.85$). The rates of the end points were also estimated with the use of the Kaplan–Meier method, and differences in those rates between the two groups were estimated by means of the log-rank test. Weibull analysis was used to estimate the projected 5-year survival of the cohort.¹⁰ All P values were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. Computations were performed with the use of SAS software, version 8.2 (SAS Institute).

RESULTS

A total of 747 patients were originally enrolled, and 334 were randomly assigned to a study group. With regard to the composite primary end point at 1 year of follow-up, we demonstrated that protected carotid artery stenting was not inferior to carotid endarterectomy.

Clinical follow-up data at 3 years were available for 85.6% of the patients in the stenting group (143 of 167 patients) and 70.1% of the patients in the endarterectomy group (117 of 167 patients). Follow-up data were available for at least 30 months for 89.8% of the patients in the stenting group (150 of 167 patients) and 76.0% of the patients in the endarterectomy group (127 of 167 patients). At 3 years, the prespecified major secondary end point had occurred in 41 of the 167 patients who underwent stenting (cumulative incidence, 24.6%) and in 45 of 167 patients who underwent endarterectomy (cumulative incidence, 26.9%), for an absolute difference of -2.3% for the stenting group (95% confidence interval, -11.8 to 7.0 ; $P=0.71$) (Table 1 and Fig. 1A). In the interval between 1 and 3 years, an additional 21 patients in the stenting group and 13 patients in the endarterectomy group had events (Fig. 2A).

Most of the increase in major adverse events between 1 and 3 years was accounted for by deaths, the majority of which were from non-neurologic causes (Table 1 and Fig. 1B). In the interval between 1 and 3 years, there were 19 additional deaths in the stenting group and 14 additional deaths in the endarterectomy group (Fig. 2B). In each group, one late death occurred in a patient

Table 1. Major Adverse Events through 1080 Days.*

Event	Stenting (N=167)	Endarterectomy (N=167)	Absolute Difference for the Stenting Group (95% CI)	P Value
	no. (%) [% as estimated by Kaplan–Meier method]		%	
Death	31 (18.6) [20.0]	35 (21.0) [24.2]	–2.4 (–10.9 to 6.1)	0.68
Cardiac cause	15 (9.0) [9.8]	15 (9.0) [10.9]	0 (–6.1 to 6.1)	0.99
Neurologic cause	3 (1.8) [2.2]	4 (2.4) [2.9]	–0.6 (–3.7 to 2.5)	0.99
Other cause	13 (7.8) [9.4]	16 (9.6) [12.4]	–1.8 (–7.8 to 4.2)	0.70
Stroke	15 (9.0) [10.1]	15 (9.0) [10.7]	0 (–6.1 to 6.1)	0.99
Major ipsilateral	2 (1.2) [1.3]	5 (3.0) [3.3]	–1.8 (–7.0 to 3.4)	0.45
Major nonipsilateral	1 (0.6) [0.6]	5 (3.0) [4.1]	–2.4 (–5.2 to 0.4)	0.21
Minor ipsilateral	9 (5.4) [6.1]	4 (2.4) [3.0]	3.0 (–1.1 to 7.1)	0.26
Minor nonipsilateral	4 (2.4) [2.7]	4 (2.4) [2.8]	0 (–3.3 to 3.3)	0.99
Myocardial infarction	9 (5.4) [6.1]	14 (8.4) [9.4]	–3.0 (–8.4 to 2.4)	0.39
Q-wave	0	2 (1.2) [1.2]	–1.2 (–2.8 to 0.5)	0.50
Non–Q-wave	9 (5.4) [6.1]	12 (7.2) [8.2]	–1.8 (–7.0 to 3.4)	0.65
Target-vessel revascularization	4 (2.4) [3.0]	9 (5.4) [7.1]	–3.0 (–7.1 to 1.1)	0.26
Prespecified major secondary end point	41 (24.6) [26.2]	45 (26.9) [30.3]	–2.3 (–11.8 to 7.0)	0.71
Excluding deaths from non- neurologic causes	15 (9.0) [9.9]	23 (13.8) [14.9]	–4.8 (–11.6 to 2.0)	0.23
Excluding myocardial in- farction within 30 days and deaths from non- neurologic causes	14 (8.4) [9.3]	15 (9.0) [10.0]	–0.6 (–6.6 to 5.4)	0.99

* CI denotes confidence interval.

previously reported to have had a procedure-related myocardial infarction. Rates of death were approximately 7 to 8% per year, with an extrapolated rate of death at 5 years of 28% (upper bound of the 95% confidence interval, 42%) for patients who underwent stenting and 35% (upper bound of the 95% confidence interval, 48%) for those who underwent endarterectomy, on the basis of fitting the 3-year data with the use of the Weibull regression equation and extrapolating to 5 years by means of simulation.¹⁰

Death was attributed to a neurologic cause in 3 of 167 patients (1.8%) in the stenting group and 4 of 167 patients (2.4%) in the endarterectomy group. Of these deaths, two in the stenting group and three in the endarterectomy group occurred after 1 year. No differences in the cause of death were apparent between the two groups.

There was a total of 15 strokes in each of the two groups at 3 years (cumulative incidence, 9.0%). These included 11 ipsilateral strokes in the stent-

ing group and 9 in the endarterectomy group, of which 4 and 1, respectively, occurred between 1 and 3 years (Fig. 2C). The Kaplan–Meier plots of freedom from stroke within 30 days and freedom from ipsilateral stroke between 31 days and 3 years essentially overlapped throughout the follow-up period (Fig. 1C).

Target-vessel revascularization was infrequent in both groups (Table 1 and Fig. 3). Revascularization mostly involved percutaneous treatment, with only one patient in each group undergoing carotid endarterectomy.

Subgroup analyses of our data were problematic, given the small numbers of patients and the fact that such analyses were not prespecified. For example, only 32 patients in the stenting group and 33 in the endarterectomy group were older than 80 years. Randomization of treatment assignment was stratified according to whether the patient had symptomatic or asymptomatic disease. There were 117 asymptomatic patients in the

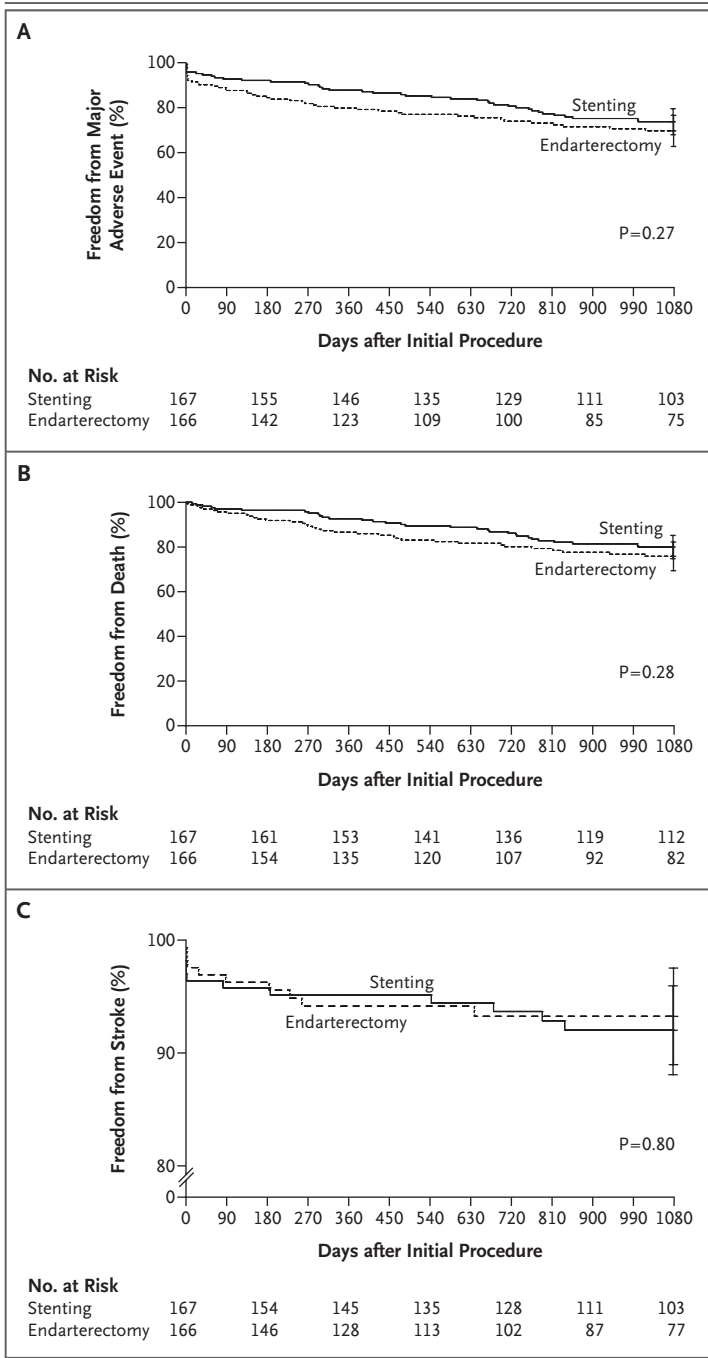


Figure 1. Kaplan–Meier Estimates for End Points, According to Treatment Group.

A total of 73.8% of patients in the stenting group and 69.7% in the endarterectomy group were free of major adverse events at 3 years (the prespecified major end point, defined as death, myocardial infarction, or stroke within 30 days or death or ipsilateral stroke between 31 days and 1080 days) (Panel A). A total of 80.0% of patients in the stenting group and 75.8% in the endarterectomy group were alive at 3 years (Panel B). A total of 92.0% of patients in the stenting group and 93.3% in the endarterectomy group were free of stroke at 3 years (defined as stroke within 30 days or ipsilateral stroke between 31 days and 1080 days) (Panel C). P values were calculated with the use of the log-rank test. I bars indicate 95% confidence intervals. Only part of the y axis is shown in Panel C.

tively. In comparison, there were only 50 patients with symptoms in the stenting group and 46 in the endarterectomy group, among whom the rates of stroke were 6.0% (3 of 50 patients) and 8.7% (4 of 46 patients) and the rates of the composite end point were 32.0% (16 of 50 patients) and 21.7% (10 of 46 patients), respectively.

DISCUSSION

We report long-term outcome data for patients with a high surgical risk who underwent either surgical or percutaneous carotid revascularization. This population was chosen because of the desire to develop a less invasive but effective treatment for patients with a high surgical risk, who account for up to one third of patients undergoing carotid endarterectomy.¹¹ We could not demonstrate a significant difference between protected carotid artery stenting and carotid endarterectomy with respect to the risk of stroke or other major adverse events in our high-risk patients at 3 years. We also found no evidence of an increased risk of repeat revascularization within 3 years after treatment.

Our data are specific to patients who are at high surgical risk, and they provide no insight into outcomes of treatment of a carotid artery stenosis in patients at low-to-moderate risk. On the basis of the similar long-term outcomes among high-risk patients in the two treatment groups, it may be tempting to infer that endarterectomy is preferable for lower-risk patients. However, this conclusion must await the reporting of randomized trials that are specifically designed and have adequate statistical power to address this question.

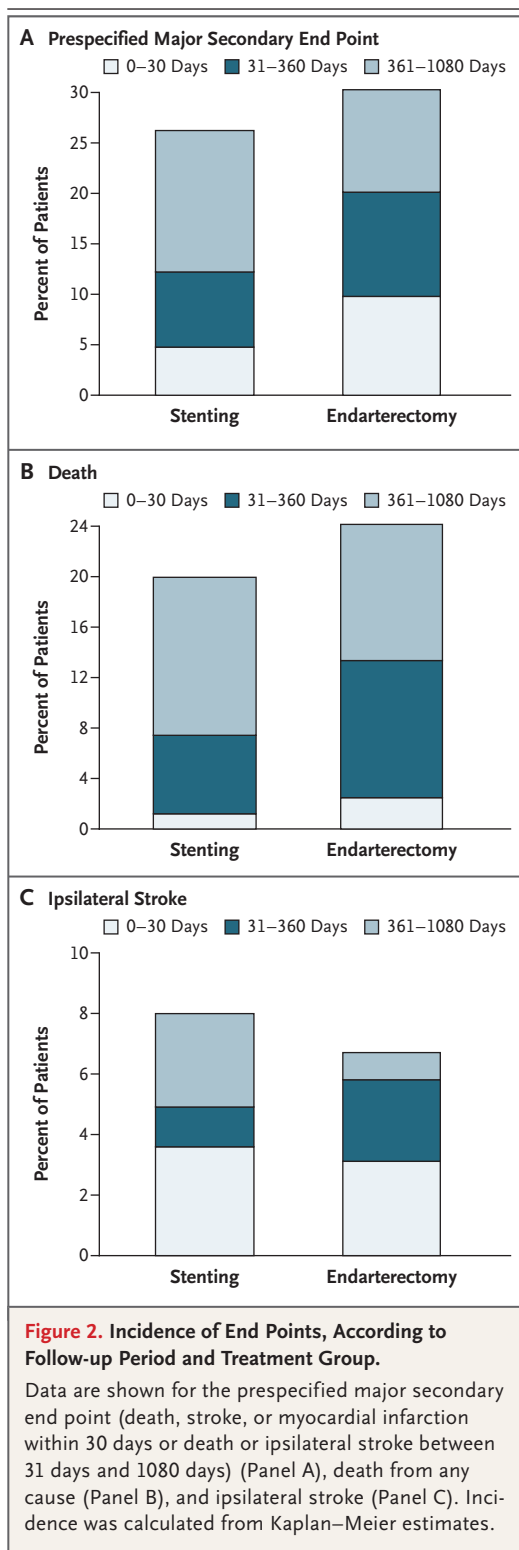
stenting group and 120 in the endarterectomy group. Among these patients, as determined in post hoc analyses, the rates of stroke at 3 years were 10.3% (12 of 117 patients) in the stenting group and 9.2% (11 of 120 patients) in the endarterectomy group, whereas the overall rates of the composite end point were 21.4% (25 of 117 patients) and 29.2% (35 of 120 patients), respec-

Patients without symptoms are an important subgroup of patients with carotid artery disease, representing 75% of patients undergoing carotid endarterectomy,¹²⁻¹⁴ and rates of stroke among asymptomatic patients with carotid stenosis of at least 80% of the luminal diameter are approximately 3.5 to 5.0% per year.¹⁵ Our trial involved too few patients with asymptomatic disease to permit any conclusions regarding the relative benefit of intervention in this subgroup. Although a benefit of either invasive strategy over current medical therapy may be uncertain for these high-risk, asymptomatic patients, we did not test this assertion; our patients were selected on the basis of referral for planned revascularization.

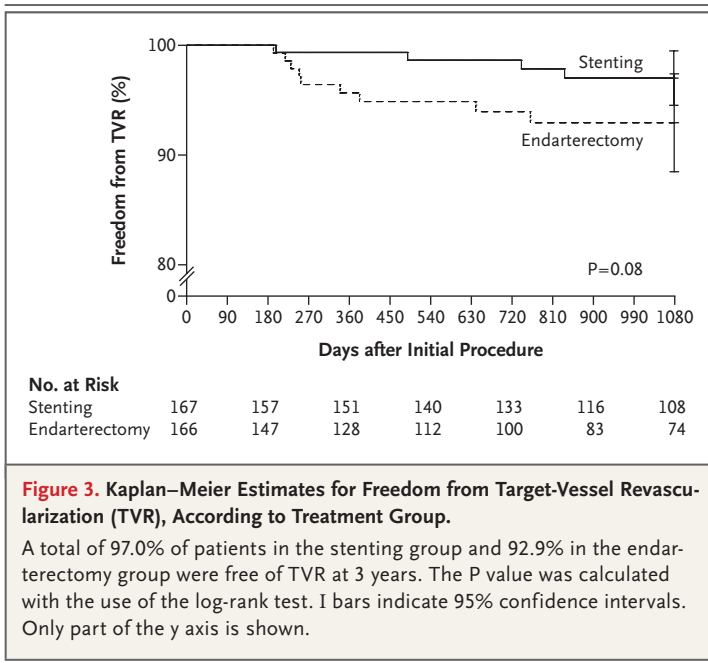
The cumulative incidence of death in our study is substantial, since the patients were elderly and many of them had coexisting conditions that are recognized to be associated with an increased risk of death among patients with carotid disease.¹⁶ Almost all deaths were due to cardiac or other non-neurologic causes. In our opinion, an invasive treatment for prevention of stroke is reasonable, even in a high-risk population, if the projected 5-year mortality is less than 50% and the intervention is not itself associated with an increased risk of death or other major adverse effects related to safety. According to the Weibull regression analysis, the 5-year mortality in our enrolled cohort was less than 50%. However, it may be appropriate to use a higher threshold for an invasive strategy, depending on the individual risk characteristics of patients, and medical therapy may be preferable to revascularization, a referral for which was the primary inclusion criterion for entry into our study.

To our knowledge, the only previous randomized trial evaluating long-term outcomes of endovascular therapy for carotid disease is the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).¹⁷ The CAVATAS investigators studied the outcomes among 504 patients randomly assigned to undergo carotid endarterectomy or endovascular therapy; they did not find a significant difference in the incidence of stroke at 3 years. The endovascular treatment, however, lacked protection against emboli and consisted of balloon angioplasty in almost three fourths of the patients. Hence, these data cannot be extrapolated to current practice.

Unlike our study, the recently reported Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S)



(ClinicalTrials.gov number, NCT00190398)¹⁸ and Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial (Current Controlled Trials



number, ISRCTN57874028)¹⁹ showed poorer outcomes for stenting than for endarterectomy. These discordant results may be explained by the fact that the EVA-3S and SPACE studies differ from ours in numerous ways, including in the selection criteria (e.g., the EVA-3S and SPACE trials included neither patients with a high surgical risk nor asymptomatic patients), the rate of use of specific emboli-protection devices (in 92% of cases in the EVA-3S trial and 27% in the SPACE trial), and the experience level of the physician who placed the stent (in the EVA-3S trial, stents could be placed by physicians who had performed as few as five previous carotid-stent procedures or, if working under the direction of a tutor, no previous procedures).

Both the EVA-3S and SPACE studies, together with ours, point to the importance of completion of randomized trials — such as the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST; ClinicalTrials.gov number, NCT00004732) — that involve adequate numbers of low-risk and moderate-risk patients, as well as careful training and monitoring of interventional physicians and mandated use of emboli-protection devices.

The absence of a medical-therapy group in our study does not allow for the comparison of safety and efficacy outcomes with those among patients treated with current antithrombotic or lipid-low-

ering therapies. Although all patients were selected on the basis of planned revascularization, and randomization of the treatment assignment was performed by an expert panel at each site, we cannot rule out the possibility that some experts may choose medical therapy to treat this high-risk group. The small size of the randomized cohort prevents meaningful subgroup analysis and identification of characteristics of the patients or lesions that may be associated with a differential risk of adverse outcomes with stenting or surgery. Follow-up to 3 years was incomplete, and we cannot rule out the possibility that our findings would have differed somewhat if the data had been complete. The Kaplan–Meier method for the estimation of cumulative incidence partially corrects for incomplete follow-up but cannot account for possible ascertainment bias. Finally, our results may not be generalizable to the use of stents and emboli-protection devices other than those used in this study, and our findings do not apply to patients at low-to-moderate surgical risk with carotid endarterectomy.

In conclusion, in the SAPHIRE trial, we compared endarterectomy and stenting for carotid artery disease in patients at high surgical risk. We obtained follow-up data at 3 years for 78% of the participants. We did not find a significant difference in the cumulative incidence of major cardiovascular events between the two treatment groups.

Supported by Cordis.

Dr. Gurm reports being named as an inventor on patents related to carotid artery stenting; Dr. Yadav reports being the inventor of the Angioguard emboli-protection device used in the SAPHIRE trial, being a shareholder in Angioguard at the time of its purchase by Johnson & Johnson in 1999, and receiving recurring payments from Johnson & Johnson as a former shareholder of Angioguard; Dr. Fayad reports receiving consulting fees from Cordis; Dr. Katzen reports receiving payments for participation on executive or interventional management committees related to carotid-stent clinical trials from Boston Scientific, Cordis, and Abbott Vascular Devices; Dr. Mishkel reports receiving grant support from Cordis, consulting fees from Boston Scientific and Abbott Vascular Devices, and lecture fees from Abbott Vascular Devices; Dr. Bajwa reports owning equity interest in Johnson & Johnson; Dr. Ansel reports receiving product royalties from Cook and serving on advisory boards for Boston Scientific, Cordis, ev3, and Lumen Medical; Dr. Strickman reports owning equity interest in Abbott, Boston Scientific, and Johnson & Johnson and receiving consulting fees from Abbott, Cordis, and Boston Scientific; Drs. Wang and Cohen report being employees of Cordis (a Johnson & Johnson company) and owning equity interest and holding stock options in Johnson & Johnson. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The investigators in the SAPHIRE trial were as follows: **Executive Committee:** J.S. Yadav, M. Wholey, K. Ouriel, B. Katzen, P. Fayad, D. Donohoe; **Data Management and Statistical Analysis Committee:** Harvard Clinical Research Institute, Boston — L. Beck, A. Natarajan; **Clinical Events Committee:** Harvard Clinical Research Institute, Boston — J. Dashe, L. Garcia, A. Hamdan, W. Koroshetz, J. Markis; **Data and Safety Monitoring Board:** L. Wechsler (chair), F. Pomposelli, J. Orav, J. Carozza; **Principal Investigators:** Cleveland Clinic Foundation, Cleveland — P. Whitlow; Shadyside Hospital, Pittsburgh — M. Wholey, G. Eles; St. John's Hospital, Springfield, IL — G. Mishkel; St. Luke's Medical Center, Milwaukee — T.K. Bajwa, A. Ahuja; Texas Heart Institute, Houston — N.E. Strickman; Riverside Methodist Hospital, Columbus, OH — G.M. Ansel; St. Elizabeth's Hospital, Boston — K. Rosenfield, R. Shainfeld, P. Soukas; Union Memorial Hospital and MedStar Health, Baltimore — F.J. Criado; Hoag Hospital and Fountain Valley Hospital, Newport Beach, CA — S. Myla; Heart Institute of Spokane, Spokane, WA — R. Raabe; North Central Heart Institute, Sioux Falls, SD — M. Bacharach; Kaiser Permanente Medical Center, San Diego, CA — R.J. Hye; Baptist Hospital of Miami, Miami — B.T. Katzen; Hahnemann Hospital, Philadelphia — D. McCormick; Cardiovascular Institute of the South, Lafayette, LA — D. Allie, C. Walker; Washington Adventist Hospital, Takoma Park, MD — F.A. Shawl; Mission Hospital Vascular Institute and Stroke Center, Mission Viejo, CA — J. Belleville; University of Alabama at Birmingham, Birmingham — C. Gomez, M. Liu, S. Saddekni; St. Luke's Medical Center, Phoenix, AZ — R.R. Heuser; St. Joseph's Medical Center, Stockton, CA — H. Madyoon; Greenville Hospital System, Greenville, SC — T.M. Sullivan, B. Gray; Lenox Hill Hospital Center, New York — G. Roubin; Our Lady of the Lake Regional Medical Center, Baton Rouge, LA — P.M. Davis; St. Francis Medical Center Hospital, Roslyn, NY — G. Petrossian; Millard Fillmore Hospital, Buffalo, NY — L.N. Hopkins; Swedish Heart Hospital, Seattle — W. Gray; Ochsner Clinic, New Orleans — S.R. Ramee; Abbott Northwestern Hospital, Minneapolis — M. Myers, D. Tubman; Montefiore Medical Center, Bronx, NY — T. Ohki.

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